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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/922,958	08/07/2001	Lorenz Poellinger	3743/49008	9818

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EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 08/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/922,958	**Applicant(s)** POELLINGER ET AL.	
	Examiner Brandon J. Fetterolf, PhD	**Art Unit** 1642	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 06 July 2006 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *33,35,36 and 40-42*.

   Claim(s) withdrawn from consideration: *1-32, 37-39 and 43-66*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 07/06/2006 in response to the previous Final Office Action (03/03/2006) is acknowledged, but has not been entered because entry of the amendment would result in a new search of the prior art, with respect to SEQ ID NO: 5 and 6, as well as, new grounds of rejection under 112 1st paragraph, New Matter and 112, 2nd paragraph.

Claims 1-33 and 35-66 are currently pending

Claims 1-32, 37-39 and 43-66 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 33, 35-36 and 40-42 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-42 **remain** rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the instant case, claim 40 is drawn to a method of evaluating an antagonist of the PYI motif or a protein encoded by one of SEQ ID NO:s 4, 5, or 6. However, the sequence represented as SEQ ID NO: 4 and 5 are amino acid sequences and not a nucleic acid sequence which encodes a protein. Thus, it is unclear what applicants are attempting to claim.

Claim 40 recites the limitation "said target protein" in claim 40. However, after careful review of the pending claims there does not appear to be a recitation of a target protein. As such,

there is insufficient antecedent basis for this limitation in the claim. It is suggested that the limitation "target protein" be amended to recite the SEQ ID NO: 2.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 33 and 35-36 **remain** rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. As set forth previously, "an isolated protein according to claim 29" is the isolated polypeptide of Claim 1 comprising an amino acid sequence of SEQ ID NO: 4 and fragments thereof with an altered PYI motif at residues 564-566. In the instant case, claims 33-36 are inclusive of a genus of molecules identified as comprising an amino acid sequence set forth in SEQ ID NO: 4 or any fragments and/or mutants thereof that bind to a genus of target proteins and fragments thereof referred to as "VHL". While claims 40-42 are inclusive of a genus of molecules referred to as having a "PYI motif" or functional fragments thereof and a genus of molecules referred to as "P564 spanning protein" or functional fragments thereof. However, the written description only sets forth two fragments of SEQ ID NO: 4 (SEQ ID NOs: 5 and 6), each of which comprise a PYI motif or p564 spanning protein, used together with VHL (SEQ ID NO: 2) for methods of identifying agents.

The specification teaches (page 9, paragraph 0026-0027) that methods for identifying agents of the present invention includes, but is not limited to, polypeptides having at least an amino acid of SEQ ID NO: 5 (minimum N-TAD) or a smaller fragment thereof, SEQ ID NO: 6 (residues 547-575), or described mutants thereof and the VHL protein (SEQ ID NO: 2). With regards to the mutants, the specification teaches (Pages 6-7) that the mutants comprise altered amino acid residues such as; an altered PYI motif at residues 564-566, a ^{564}P, a $^{565\text{-}566}$YI, ^{565}Y, a $^{569\text{-}571}$DDD, ... ect.. The specification further teaches (page 13, paragraph 0042) that additional methods for identifying agents of the invention include, but are not limited to, polypeptides comprising a PYI motif or p564

spanning polypeptide (residues 547-575) or portion thereof. Thus, it appears that a p564 spanning polypeptide consists of the same amino acids as disclosed for SEQ ID NO: 6. However, the written description only sets forth two fragments of SEQ ID NO: 4 (SEQ ID NOs: 5 and 6), each of which comprise a PYI motif or p564 spanning protein, used together with VHL (SEQ ID NO: 2) for identifying agents. Therefore, the written description does not commensurate with the full scope of any fragments and/or variants of SEQ ID NO: 4 or any fragments of the VHL protein (SEQ ID NO: 2).

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or by describing structural features common the genus that "constitute a substantial portion of the genus." See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997): "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNA, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus."

The court has since clarified that this standard applies to compounds other than cDNAs. See University of Rochester v. G.D. Searle & Co., Inc., __F.3d__,2004 WL 260813, at *9 (Fed.Cir.Feb. 13, 2004). The instant specification fails to provide sufficient descriptive information, such as definitive structural or functional features that are common to the genus. That is, the specification provides neither a representative number of molecules that bind VHL nor does it provide a description of structural features that are common to SEQ ID NO: 4. Further, the specification fails to provide a representative number of molecules referred to as VHL along with a description of structural features that are common to the VHL. Thus, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure(s) of all the

fragments of SEQ ID NO: 4 and VHL, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a VHL protein (SEQ ID NO: 2) and two fragments of SEQ ID NO: 4,(SEQ ID NOs: 5 and 6), which comprise the PYI motif and p564 spanning protein, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

In response to the rejection, Applicants contend that the claims have been amended which are believed to obviate this rejection. Specifically, Applicants assert that the claimed invention relates to SEQ ID NO: 2 and specific fragments thereof, namely SEQ ID NO: 5 and 6.

As, Applicant's arguments appear to be solely drawn to the claims as presently amended, but not entered, such arguments have not been considered.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 40-42 remain rejected under 35 U.S.C. 102(b) as being anticipated by Maxwell et al. (Nature 1999; 399: 271-275, IDS).

Maxwell discloses a method of evaluating an antagonist of the PYI motif for VHL-HIF-1 alpha interacting inhibiting efficacy; comprising: determining a reference level of VHL-HIF-1 alpha

interacting in a cell or group of cells; administering said antagonist to an equivalent test cell; measuring the level of VHL-HIF-1 alpha interaction in said test cell; and determining said antagonist is efficacious when the measured test level of VHL-HIF-1 alpha interaction is less than the reference level of VHL-HIF-1 alpha interaction (page 273, 1st column, 1st full paragraph to 2nd column). The reference further teaches that the test were done at both normoxic and hypoxic conditions (page 273, 1st column, 1st full paragraph to 2nd column). Thus, while the Maxwell et al. does not specifically state that the inhibitor is an agonist of the PYI motif, the claimed functional limitation would be an inherent property of the referenced method because as evidenced by Tanimoto et al. (EMBO 2000; 19: 4298-4309, IDS), the highly conserved core motif, i.e. PYI, of the N-TAD of HIF-1 alpha is critical for interaction with VHL (specifically page 4303, 1st column, 1st full paragraph). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Therefore, NO claim is allowed

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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